When is Magnetic Resonance Imaging most beneficial in olfactory dysfunction? A retrospective review of a tertiary referral smell and taste clinic

Short Title (within 40 characters): **Role of MRI in Olfactory Dysfunction**

Abstract:

Background

Olfactory dysfunction (OD) is a common but underreported problem that can significantly impact a patient's quality of life. Dysfunction is prevalent in over 5% of the adult population and can be broadly categorised into conductive and sensorineural causes. Magnetic Resonance Imaging (MRI) can form part of the diagnostic work up, although its exact role is often debated.

Objectives

The aim of this study was to evaluate the value of MRI in managing patients with OD.

Design/ Method

A retrospective analysis of the records of patients presenting to national smell and taste clinic over a five-year period was performed. Variables included demographics, endoscopic findings, final diagnosis, psychophysical smell test and MRI results.

Results

A total of 409 patients underwent clinical assessment and smell testing, of which 172 patients (42%) had MRI scans. The age range of patients was 10 to 93yrs. Imaging in younger age-groups

was associated with a higher rate of positive findings, however identifiable causes for OD were recorded across the range. MRI provided both diagnostic and prognostic information in those with idiopathic, traumatic, and congenital causes of OD. For example, MRI provided information on the extent or absence of gliosis in those with a head trauma history allowing further treatment and prognosis.

Conclusion

We recommend the adjunct use of MRI in patients with a clear history and examination findings of head injury, congenital cases and in apparent idiopathic cases. MRI should be requested to compliment clinical findings with a view to aiding decision-making on treatment and prognosis independent of patient's age.

Key points:

1. MRI scans are often requested when assessing patients with OD but without a clear rationale for how that will influence the management.
2. Assessment of patients with OD includes a careful history, examination and psychophysical smell test to determine what, if any, further investigations are needed.
3. MRI in children for OD showed higher incidence of positive findings suggesting a low threshold to use MRI for investigation in children.
4. MRI used as an adjunct, in correctly selected cases, can help guide treatment and prognosis when used in the right patient.
5. We recommend use of MRI as adjunct in cases of post traumatic olfactory dysfunction, suspected congenital cases and in any apparent idiopathic cases to aid treatment and management; MRI should not be requested primarily in cases of post-infectious olfactory dysfunction or chronic rhinosinusitis.

Keywords: Olfactology, Smell and Taste Disorders, MRI, Olfactory Dysfunction, Anosmia, Smell, Olfactory Nerve Disorders, Olfactory Nerve Injuries.

Introduction:

Olfactory dysfunction (OD) is a common yet under-reported problem; persistent symptoms of anosmia affect 1-5% whilst hyposmia and other smell disturbances affect up to 20% of the population increasing in those over the age of 60yrs[1-3]. The main causes include chronic rhinosinusitis (CRS) and post-infectious olfactory dysfunction (PIOD). Other causes include head trauma (PTOD), neurological disease (including Alzheimer's and Parkinson's disease) where symptoms are more likely to be permanent[4, 5] and in rare cases it may be due to congenital aplasia or neoplasms including olfactory meningiomas and estheoneuroblastomas. Patients describe symptoms including anosmia (complete loss of smell), parosmia (smell distortion), phantosmia (smell hallucination) and perceived dysgeusia (taste disturbance) or ageusia (taste loss). Dysfunction can be life changing, impact employment, safety, general enjoyment, and quality of life[6, 7].

Clinical investigation requires a thorough history and examination alongside psychophysical testing to determine the most likely pathology. Initial assessment may be followed by imaging, such as magnetic resonance (MRI) and/or computerised tomography (CT) and blood tests[8].

Although guidelines for the initial management of OD exist[5], there remains controversy over the role of MRIs; when and in which patient should it be used to provide most benefit and is it cost effective[9] This debate is driven by societal factors, finite resources, and budgetary constraints of health care systems. Majority have argued against routine use of MRI. Contradicting studies have concentrated on medicolegal arguments of a misdiagnosed neoplasm. Powell et al suggested that many patients with isolated olfactory loss are scanned unnecessarily and referencing the

more elderly cohort they argue any positive findings would not significantly alter clinical management[10]. Understandably intracranial neoplasms remain the diagnosis that both specialists and patients are most concerned about and likely remains a drive for imaging. One study having modelled the societal economics of MRI in Idiopathic Olfactory Dysfunction (IOD) concluded that the most cost-effective decision was to omit routine MR imaging during the diagnostic workup[9]. But aside from rule out neoplasia, MR imaging also allows us to determine the level and extent of structural change, confirm or discount certain diagnoses, ensure treatment is appropriately targeted and that patients are guided on the probability of recovery.

Objectives:

This study aimed to review MRI findings when used in a tertiary chemosensory disorders clinic to characterise the indications, findings, and utility of MRI in the investigation and management of olfactory dysfunction.

Methods:

Study design and setting

This study was conducted as a retrospective review of the clinics database and case notes of 409 consecutive patients presenting to a tertiary referral smell and taste clinic over a five-year period (2014-2019). Attending patients are recorded into a prospective database alongside their smell test results providing an accurate patient cohort.

Eligibility criteria

Inclusion criteria:

Patients presenting to the tertiary referral smell and taste clinic, with any cause of OD.

Adults and children able to independently complete a smell test.

Exclusion criteria:

Incomplete smell test data.

Any patients lost to follow up where there is no clear final diagnosis.

Variables

Information on patient demographics, clinical history and examination findings, olfactory test scores, the choice and results of any imaging modalities and final diagnosis were collated. All patients attending the smell and taste clinic undertake olfactory questionnaires[11] and smell testing prior to clinical assessment. Psychophysical olfactory testing is undertaken using the Sniffin' Sticks test (Heinrich Burghardt®, GMBH, Wedel, Germany) which has been validated in the UK [12] to determine the threshold, discrimination and identification scores with the combined TDI score ranking the patients as either normosmic, hyposmic or functionally anosmic[13].

Patients are specifically questioned on the presence of nasal symptoms, allergy, other medical comorbidities, and medication use. With respect to the OD, information on the timing, duration and precipitants are sought including specifically any association with head trauma, chemical exposure, or preceding viral illness. Routine endoscopy is performed on all patients with a 30-degree rigid nasendoscope to assess for the presence of underlying anatomical, inflammatory and/or infective processes. Any further investigations are directed by clinical findings and suspected underlying cause, with the final diagnosis overseen by a lead olfactologist. CT imaging is obtained when there is suspicion of olfactory cleft stenosis (OCS) or CRS. MRI is not routinely

obtained in patients that provide a clear history of olfactory loss secondary to viral illness. All imaging is reported locally by an experienced neuro-radiologist whilst images from external units are transferred to our unit, often without a formal report and are subsequently assessed by the lead olfactologist in clinic with review by the local neuro-radiologist as required.

Results:

Patients were grouped by final diagnosis into those with evidence of CRS, PTOD, PIOD, IOD, congenital olfactory aplasia, OCS and 'other' cohort. There were no reported findings of neoplasms and the category 'other' included cases of rhinitis, hypopituitarism, toxic rhinitis and iatrogenic (post-surgical).

Gender and age distribution in diagnostic groups is summarised in Table 1 and Graph 1. Of the total 409 patients, 59.6% (n=244) were female and the average age for the entire cohort was 51yrs (range 10 to 93yrs). Patients were analysed in age brackets of approximately 10-year intervals (0-10, 11-19, etc); the most common age range of presentation occurred between the age of 50-69 years. Within this cohort the commonest diagnosis was CRS (35.8%) followed by PIOD (23.4%) and IOD (19%). Conversely the commonest diagnoses in younger ages (11-29yrs) were OCS (28%) and congenital anosmia (28%) (Graph1). There were no cases of IOD before 40yrs, this diagnosis steadily increased with age peaking in the 60–69-year cohort. Average TDI scores varied according to diagnostic groups (Graph 2); patients with PIOD had a higher TDI score (mean =18.13) compared with PTOD (mean 13.78) and IOD (mean=13.84).

One hundred and seventy-two patients (42%) underwent MRI imaging as part of their diagnostic work up either locally or at referring hospital; the commonest findings are highlighted in Table 2. All MRIs followed a standardised protocol which includes a T2 coronal sequence through the olfactory bulbs. The largest cohort with MRIs was between 50-69 years, of which 46-50% had

positive findings. Imaging in younger age groups was associated with a higher rate of positive findings; 63-68%, dropping to 40-46% in those 60-79yrs and 20% in 80yrs and above.

In patients with congenital anosmia, MRI confirmed either aplasia of the olfactory bulbs in the majority of cases and in one case demonstrated significant OCS, which was subsequently treated. In patients with OCS, 65.38% had undergone MRIs, mostly by referring hospitals, initially considered to be idiopathic. Only 3 patients (17.64%) demonstrated reduced bulb volume and 29.4% of MRIs reports successfully highlighted OCS.

All patients with trauma history underwent MRI with 58.6% demonstrating gliosis and just under 6.89% encephalomalacia (Fig 1A). A third of trauma patients had an anatomically normal MRI with no evidence of gliosis or scarring, and the remaining demonstrated reduced bulb volume (Table 2); the latter may imply the level of injury lies at the olfactory fila due to shearing forces. In the idiopathic subgroup, 65.67% of imaged patients had a normal MRI, 26.86% were reported to have reduction in olfactory bulb volume (OBV) and one patient had brain atrophy without a neurological diagnosis.

Patients with CRS or with a PIOD history and normal examination are not routinely MR imaged, however 15 CRS patients had already undergone MRI externally, the vast majority of which were reported as normal or in keeping with CRS (See table 2). A total of 14 patients with PIOD had also undergone external MRIs, with 92.8% of scans reported as normal. In these two patient groups, a reduction in OBV was reported in 26.6% and 7.2% respectively.

Discussion:

Key results:

Identifiable causes for OD were identified in all patient cohorts. Our results highlight that in certain subgroups, namely congenital, PTOD and IOD, MRI can be a useful diagnostic adjunct. MRI can

confirm a suspected diagnosis or suggest alternate pathology for example OCS in suspected congenital aplasia. It also provides prognostic information, allows a more accurate consultation on therapeutic interventions and recovery. These benefits of MRI appear to persist in older cohorts, despite the overall number of positive findings on MRI reducing with age.

Limitations**:**

The study cohort consisted of patients referred to a tertiary clinic from centres around the UK. Although representative of a diverse UK population, our analysis may represent a self-selecting group of patients that sought further investigation and tertiary referral. This study was a retrospective analysis working from a known final diagnosis. Since the final IOD cohort in this study does not include those patients who were initially considered idiopathic it limits our ability to analyse the diagnostic role of MRI in patients with suspected IOD. Patients attending our clinic were imaged according to our clinic guidelines and thus patients with CRS and PIOD were not imaged. The resulting selection bias accounts for the lower number of MRIs in these cohorts.

Interpretation:

Clinical history and examination remain crucial to directing further investigation in SATDs. Imaging provides a complementary tool to investigate patients with OD in addition to psychophysical chemosensory testing. Previous studies have argued that routine MRI scanning adds little value to the overall management of patients with OD[10, 14]. Powell et al demonstrated olfactory tract related abnormalities in 6% of MRIs in their cohort, concluding that these findings did not alter management bar one case of esthioneuroblastoma[10]. In other words, 99% of scans made no impact on the final patient management, they argued that most scans simply provided the patients

with an explanation. Our study however highlights that when performed in the right patient, MRI provides both diagnostic and prognostic information.

Powell et al also postulated that children and younger adults with OD were more likely to have an identifiable cause for their symptoms than the elderly, in whom they felt imaging could be avoided[10]. However, in our largest cohort of OD patients aged 50-69yrs, only 19% were classed as truly idiopathic, the other 81% had identifiable pathology (Graph 1). Interestingly this cohort also included 2 cases of undiagnosed olfactory aplasia, that had initially been regarded as IOD. MRI provided prognostic/diagnostic information in 46% of patients aged 60-69yrs, 40% in those 70-79yrs of age, dropping to 20% in those 80yrs and above. This included 3 patients with PTOD, within whom MRI demonstrated normal findings and hence possibility for recovery.

Analysing MRI outcomes by age has clarified that despite an overall reduction in pathological findings there remains a wide variety of diagnoses that occur within older patients (Graph 3). The highest peaks for diagnosing both PTOD and IOD were within the 60–69-year age cohort. Decker et al reported that MRIs demonstrated evidence of an underlying cause in 1 out of every 4 “IOD” patients in their study[9], the most common finding being frontoethmoidal sinusitis undiagnosed on clinical examination. A true diagnostic pickup rate of 25% within “IOD” patients, which in our study occurred exclusively in older cohorts would lend support to the regular use of MRI. The MRI results for our IOD cohort however simply found reduced OBV as the commonest finding. This may be due the limitation of our retrospective study. Olfactory cleft stenosis (OCS) is a fixed anatomical abnormality causing significant narrowing and is best visualised with CT imaging if evidence is seen on MRI.

OD is estimated to affect approximately 5-10% of patients who have suffered a significant head injury[15]. Patient with fronto-occipital trauma appear particularly prone. According to Howell et. all, there are three main underlying mechanisms: cribriform plate injury, sinonasal tract disruption and focal contusion or haemorrhage within the olfactory cortex[15]. The extent of cortical scarring

can be demonstrated on MRI, where findings of extensive frontal gliosis is seen in (FIG 1A), indicate a more limited chance of recovery, and emphasis can be directed on patient safety and education. MRI cannot establish whether there has been irreparable shearing olfactory axon damage, however where there is no visible scarring it remains possible that some neuronal recovery may occur and hence a role for targeted intervention. Recovery of function will depend on the degree of injury, with several studies demonstrating improvement rates of between 10-35% on subsequent olfactory testing[16-18] and whilst most recover within 2 years[15, 19], a small but not insignificant proportion experience recovery beyond this[20].

Congenital anosmia remains rare, affecting 1% of the anosmic population with both syndromic (CHARGE, Kallmann syndrome) and non-syndromic causes (Cystic fibrosis)[21, 22]. In Kallmann syndrome, MRI can demonstrate absence of both olfactory bulbs, tracts and sometimes olfactory sulcus[23]. Hauser et al conducted a retrospective review of OD at a tertiary paediatric hospital and found similar results to that in adults, rhinological disease accounted for over 40%, IOD a further 40%, with congenital causes making up just over 10% followed by traumatic and neoplastic at 2.7% each[22]. In our study all patients with suspected congenital anosmia reported a clear history of never being able to smell, lacked clinical evidence of obvious OCS and were categorised as anosmic on smell testing. Subsequent MRIs revealed aplasia of the olfactory bulbs (Fig 1B) in all but one who demonstrated OCS. A few patients with congenital loss presented over the age of 40 years which highlights the general lack of awareness of OD amongst the general public and medical profession.

Neoplasms around the cribriform plate can be associated with OD, the commonest lesions include olfactory neuroblastomas and planum sphenoidale meningioma. These tumours remain exceedingly rare with only 1000 cases of olfactory neuroblastoma having been reported since being first described in 1924[24].

In our patient cohort we did not come across any tumours as the cause of OD. This may be due to the referral bias and need for urgent treatment on identification. Given their rarity we would not advocate for routine imaging to 'rule out' an underlying tumour unless there is strong clinical suspicion such as a nasal mass on examination.

Generalisability:

Our patient cohort comprised of individuals referred from centres all around the UK, the diagnoses observed therefore represents a diverse patient-group geographically. OD remains an under-diagnosed problem. Milder cohorts may be underrepresented within this analysis. The current recommendation from our study is that MRI has a select role in the investigation of OD, its use should not be determined by the patient's age but instead the working diagnosis. MRI should be requested to compliment clinical findings and aid decision making in treatment choices. In those patients with a normal clinical examination and clear aetiology such as OD following a viral infection, we concur with other authors that imaging is not necessary[5]. MRI as a screening tool can burden health care systems. The potential implications of imaging most OD patients becomes apparent if one considers that each MRI scan can last between 15-90 minutes and can cost an average of £363 per scan. We currently recommend using MRI in patients with either a clear history of PTOD, congenital anosmia, apparent IOD and cases with suspicion of mixed aetiology.

Conclusion:

This analysis highlights the wide underlying issues in OD across different ages. Patients in mid to later life account for the largest population seeking treatment, in which there remains a variety of diagnoses. MRI provides a useful adjunct during investigation of patients with PTOD and suspected congenital loss independent of the patients' age; providing both useful diagnostic and prognostic information that allows for more realistic patient expectations on treatment and

recovery. MRI should not be thought of as simply a tool to ‘rule out’ a tumour, the information it provides can be used to direct investigations such as blood tests, CT imaging and neurological consults alongside treatment choices.

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	CRS	OCS	Congenital	PTOD	PIOD	IOD	other
Male (%)	74 (54.01%)	14 (53.8%)	6 (40%)	9 (31.03%)	16 (19.27%)	28 (40%)	17 (36.17%)
Female (%)	63 (45.98%)	12 (46.15%)	9 (60%)	20 (68.9%)	67 (80.72%)	42(60%)	30 (63.82%)
Total (n)	137	26	15	29	83	70	47

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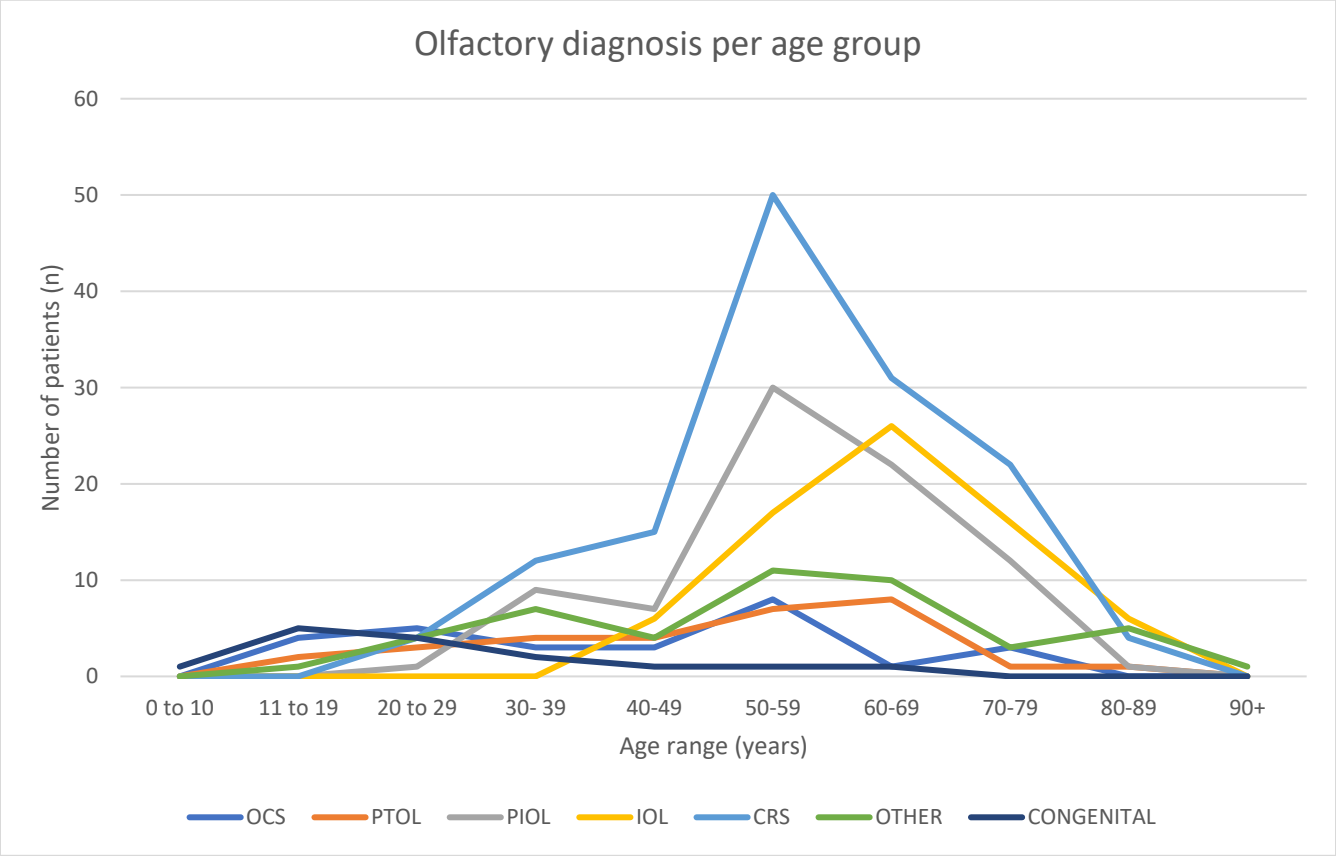
334 Table 1. Gender distribution amongst the different diagnostic categories of olfactory dysfunction
335 (percentage of patients in each category). CRS= Chronic rhinosinusitis, OCS= Olfactory cleft
336 stenosis, PTOD= Post Traumatic Olfactory Dysfunction, PIOD = Post Infectious Olfactory
337 Dysfunction, IOD = Idiopathic olfactory loss).



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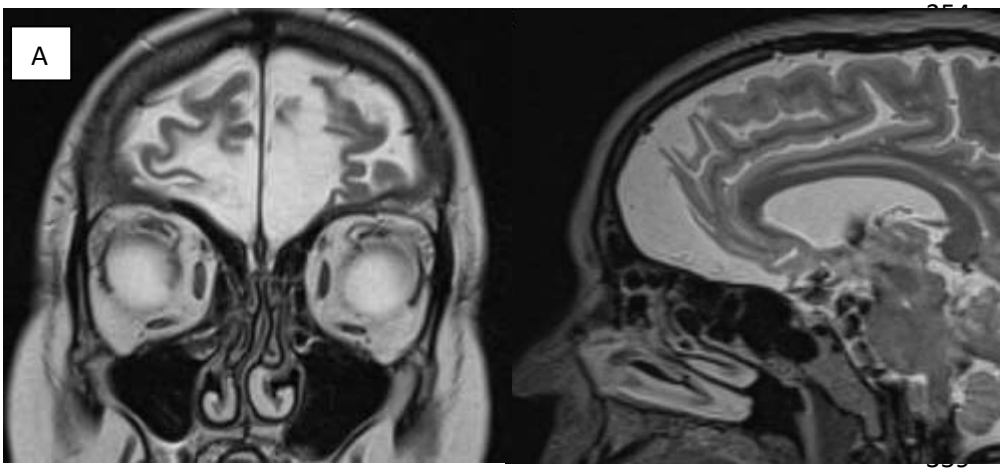
Graph.1 Age distribution amongst the different olfactory dysfunction diagnoses. CRS= Chronic rhinosinusitis, OCS= olfactory cleft stenosis, PTOD=Post Traumatic Olfactory Dysfunction, PIOD= Post Infectious olfactory dysfunction.

	CRS	OCS	Congenital	PTOD	PIOD	IOD	Other
Total number patient who underwent MRI	15	17	15	29	14	67	16
Percentage of patients who underwent MRI (Exact proportion)	20.55% (15/137)	65.38% (17/26)	100% (15/15)	100% (29/29)	16.8% (14/83)	95.71% (67/70)	34% (16/47)
Normal report (%)	8/15 (53.33%)	7/17 (41.17 %)	0/15	10/29 (34.48%)	13/14 (92.8%)	44/67 (65.67%)	10/16 (62.5%)
Medial orbitofrontal gliosis (%)	0/15	0/17	0/15	17/29 (58.62%)	0/14	0/67	0/16
Encephalomalacia (%)	0/15	0/17	0/15	2/29 (6.89%)	0/14	0/67	0/16
Reduced bulb volume (%)	4/15 (26.66%)	3/17 (17.64 %)	0/15	4/29 (13.79%)	1/14 (7.2%)	18/67 (26.86%)	4/16 (25%)

Absence of olfactory bulb/ tract (%)	0/15	0/17	15/15(100 %)	0/29	0/14	0/67	0/16
Olfactory cleft stenosis	0/15	5/17 (29.41 %)	1/15 (5.88%)	0/29	0/14	0/67	0/16
Nasal/ sinus mucosal thickening	4/15 (26.66%)	1/17 (5.88%)	1/15 (5.88%)	0/29	0/14	4/67 (5.97%)	2/16 (12.5%)
Other	-	-	-	-	-	Mild brain atrophy 1/67 (1.49%)	Mild brain atrophy 1/16 (6.25%)

Table 2. Total number of MRI scans performed per diagnostic criteria and breakdown of significant findings. (CRS= Chronic rhinosinusitis, OCS= Olfactory cleft stenosis, PTOD= Post Traumatic Olfactory Dysfunction, PIOD = Post Infectious Olfactory Dysfunction, IOD = Idiopathic Olfactory Loss).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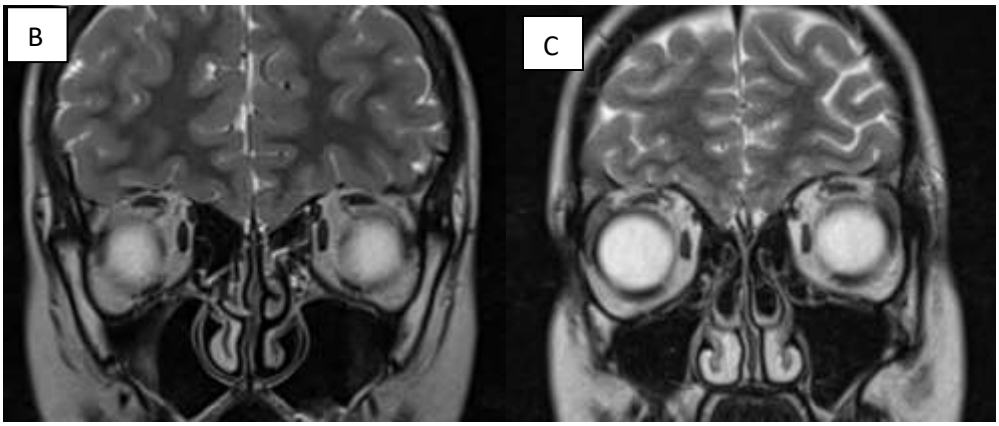
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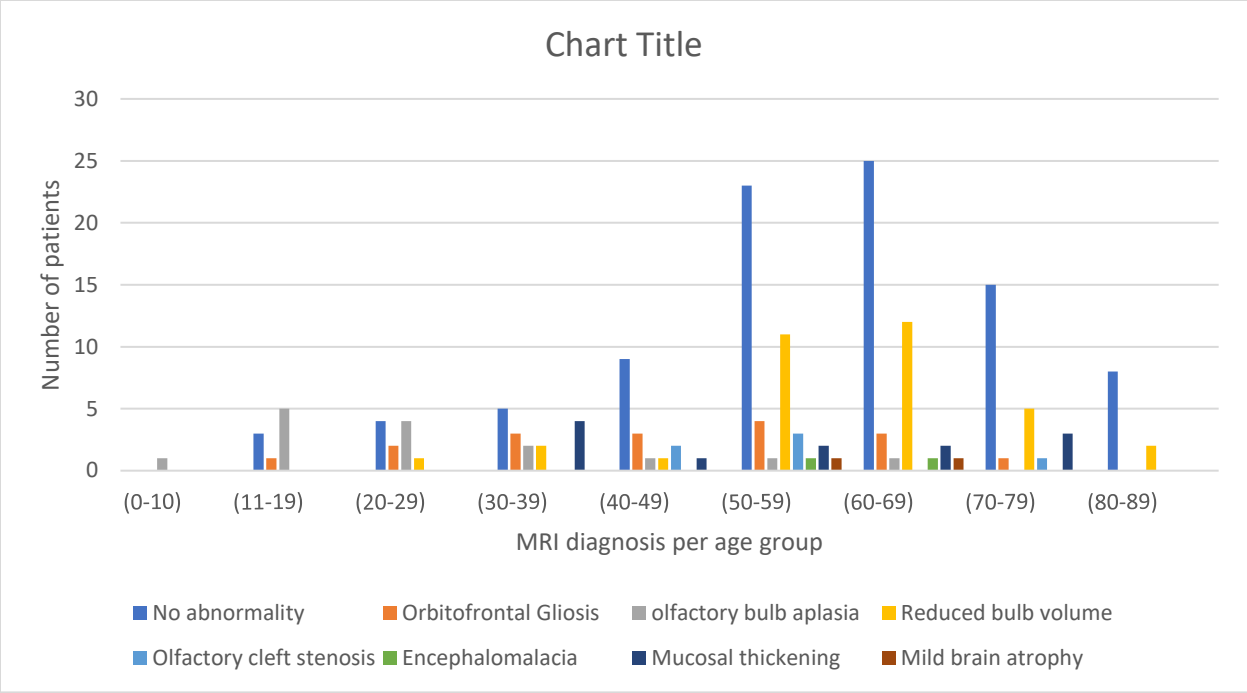
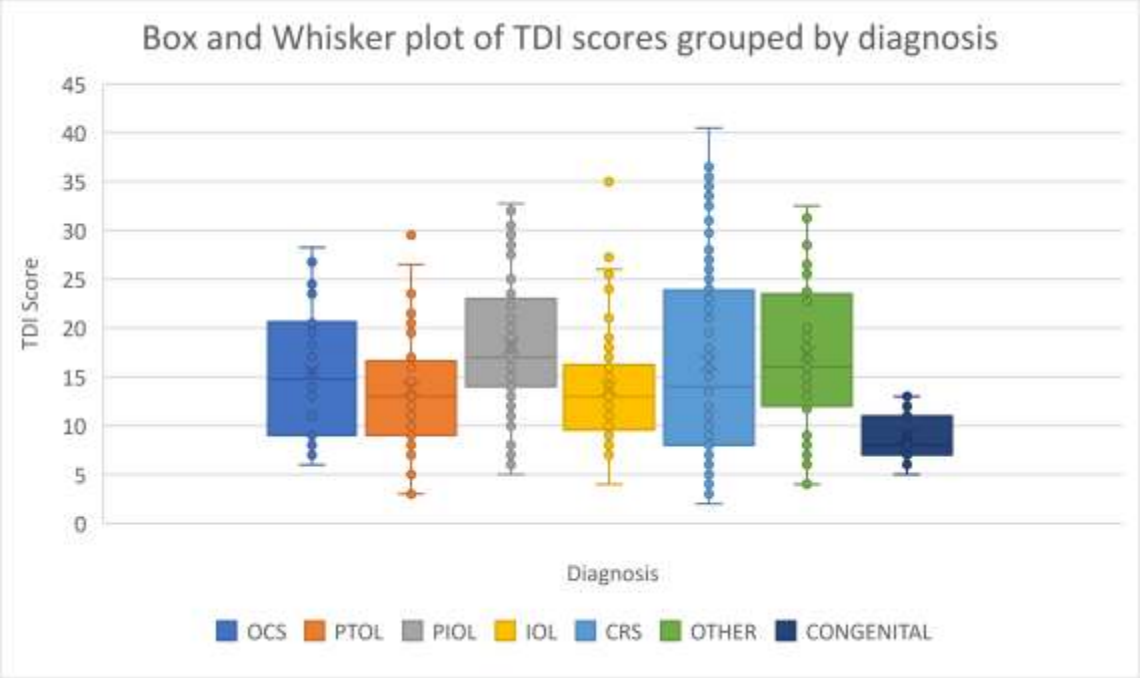
Fig 1. A) Coronal and sagittal T2 weighted MR imaging demonstrating extensive gliosis in an anosmic patient who had sustaining a significant head injury the previous year. B) Coronal T2 weighted MR imaging demonstrating hypoplastic olfactory bulbs in a child with congenital anosmia. C) Coronal T2 MR images demonstrating OCS secondary to an anatomical narrowing with a medialised middle turbinate and concha bullosa. OCS can be clearly demonstrated on both CT or MR imaging and within our cohort was highlighted in some patients during their initial workup for idiopathic anosmia.



Graph 3. The total number and age distribution of each specific MRI finding within the patient cohort.



Graph 2. Box and whisker plot of individual smell test (TDI) scores per patient, divided into diagnostic groups. (CRS= Chronic rhinosinusitis, OCS= Olfactory cleft stenosis, PTOD= Post Traumatic Olfactory Dysfunction, PIOD = Post Infectious Olfactory Dysfunction, IOD = Idiopathic olfactory loss).